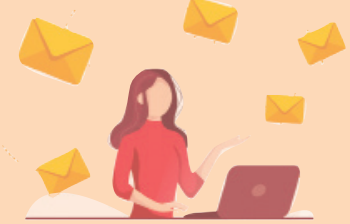
Letters to the Editor



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FRONTIERS IN DETECTING CONSCIOUSNESS: THE GROWING USE OF EEG ANALYSIS

Dear Editor:

There is growing scientific interest regarding the use of electroencephalogram (EEG) and multivariate analysis as a means to classify states of consciousness. A recent work assessed the validity of 28 potential EEG markers of consciousness, using the Disorders of Consciousness (DoC)-Forest (the name of the algorithm) tool, to establish states of awareness in a large population of patients with unresponsive wakefulness syndrome (UWS) or minimally conscious state (MCS).[1] Using the DoC-Forest approach, the authors demonstrated that combining multiple EEG data (including alpha-band power, theta-band connectivity, and time series complexity) in the analysis provides complementary information to clinical assessments of states of consciousness, significantly reducing the influence of different EEG configurations and experimental protocols on the distribution and performance of the EEG markers. The gold-standard approach for diagnosing a consciousness disorder is repeated clinical assessment using the Coma Recovery Scale (CRS-R).[2,3] However, even the best standardized behavioral assessments can miss signs of residual conscious processing in some patients. Using advanced para-clinical approaches, these signs are more easily detected,[4,5] and the patients may be labeled as "with covert awareness" or "with cognitive-motor dissociation."[6,7] We have shown that different experimental approaches based on EEG data are useful in refining the clinical diagnosis in cases of consciousness,[8,9] as recently as that proposed by Engemann et al.[1] As the authors confirmed, the DoC-Forest complex analyses tool consistently demonstrated its usefulness in differentiating states of consciousness.

EEG analysis offers rich temporal information on cognitive operations, capturing even small fluctuations in awareness, which are not only biasing factors when attempting to differentiate disorders of consciousness, but are important predictors of awareness recovery.[10] Additionally, EEG analysis using DoC-Forest could potentially be used at bedside or during home assessment. The authors highlight the importance of approaching EEG markers with DoC-Forest. Quantitative metrics of specific neural networks have been shown to correlate with the continuum of behavioral recovery in patients with disorders of consciousness (from UWS to locked-in syndrome).[11] We recently demonstrated the usefulness of combining different network metrics to further refine the correlation between EEG connectivity and behavioral recovery.[12] Specifically, this multivariate approach was shown to better characterize the primary pathophysiological features of (un)awareness, including involvement of the interhemispheric fronto-parietal functional connectivity and the aberrant connectome organization, at both network topology and nodal level.[13]

In conclusion, evidence supporting the use of EEG and the multivariate approach in the differential diagnosis of consciousness disorders is growing. Indeed, analyzing combinations of markers (either neurophysiologically or through neuroimaging) synergistically outperforms the univariate approach, complementing behavioral assessment and reducing the rate of misdiagnosis in patients with consciousness disorders. The DoC-Forest approach can help better identify patients who require further assessments, as well as estimate prognosis and track patient response to interventions.

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With regards,

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ROLE OF NOREPINEPHRINE IN SCHIZOPHRENIA: AN OLD THEORY APPLIED TO A NEW CASE IN EMERGENCY MEDICINE

Dear Editor:

A number of hypotheses have been put forth regarding the etiology of schizophrenia, including dopamine hypothesis and glutamate hypothesis.[1] However, a lesser known theory is that elevated norepinephrinergic signaling plays a causative role in schizophrenia.[2] We treated a patient with septic shock schizophrenia who developed delusions and hallucinations following continuous norepinephrine infusion. This phenomenon provides additional evidence supporting the theory that norepinephrine plays

an important role in the pathophysiology of schizophrenia.

Case report. A 71-year-old female patient with schizophrenia was transferred to our hospital for treatment of pyrexia and hypotension. She had a 40-year history of chronic paranoid schizophrenia, which had been successfully treated with quetiapine of 400mg/day for the past eight years prior to this admission. Her initial vital signs included a temperature of 39.6°C, blood pressure (BP) of 54/30mmHg, heart rate of 128 beats/min, respiratory rate of 24 breaths/min, and oxygen saturation of 90 percent while breathing ambient air. Her abdomen was distended without rebound tenderness. Abdominal computed tomography revealed marked dilatation of large intestine without mechanical obstruction, suggesting megacolon. Aggressive fluid resuscitation was initiated, and blood cultures obtained. Intravenous meropenem was initiated, based on suspicion of possible bacterial translocation from dilated colon. The blood culture revealed *Escherichia coli* within 24 hours. She was diagnosed as having septic shock due to megacolon. According to treatment guidelines for septic shock,[3] the patient was administered norepinephrine 0.03µg/kg/min, which was increased to 0.2µg/kg/min, to maintain blood pressure. However, the patient became irritable and developed symptoms of psychosis, including delusion and hallucination. Norepinephrine was discontinued, and dopamine was initiated at 5µg/kg/min and increased to 8 to 10µg/kg/min, which successfully maintained her systolic BP at 90 to 110mmHg and improved her psychotic symptoms. The patient then developed tachycardia (>110 beats/min), resulting in the decision to discontinue the dopamine and rechallenge the patient with norepinephrine. Upon reinititation of norepinephrine, the patient began screaming loudly and re-exhibiting signs of psychosis (delusion, hallucination). Norepinephrine was once again discontinued and dopamine restarted to maintain her BP. By Day 10 in the hospital, the patient was successfully weaned off the dopamine infusion, with no exacerbation of psychosis.

Discussion. It was interesting to observe in this patient that norepinephrine, not dopamine, appeared to cause symptoms of delusion and hallucination in this patient. Moreover, rechallenging the patient with norepinephrine resulted in a return of the psychotic symptoms. In this case, the Adverse Drug Reaction Probability Scale[4] score was 5, which indicates "probable" causality between norepinephrine and psychosis. Our observations are consistent with results from a study in the late 1980s in which patients with schizophrenia who had relapsed were observed to have significantly higher cerebrospinal fluid norepinephrine levels than patients who did not relapse.[5] Researchers have hypothesized that elevated norepinephrine signaling might play a prominent role in the development of the paranoid subtype of schizophrenia, and, subsequently, that blocking norepinephrine signaling might suppress the associated symptoms.[6] A correlation between cerebrospinal fluid norepinephrine levels and severity of psychosis in patients with drug-free schizophrenia has been shown.[7] Norepinephrinergic receptors are found on nerve fibers that originate from the locus coeruleus and project to many parts of the forebrain, including the cortex, cerebellum, amygdala, hippocampus, basal ganglia, thalamus, and hypothalamus.[8] Norepinephrine signaling plays a role in a broad range of brain functions, such as arousal, stress response, and memory consolidation; thus, it seems possible that dysfunction in norepinephrine signaling could result in psychosis in some patients.

Circulating monoamines are prevented from entering the brain; however, high circulating concentrations of monoamines can open the blood–brain barrier. Once the barrier is open, systemically administered monoamines can enter the brain parenchyma and induce pronounced changes in neurotransmissions.[9] Thus, a continuous infusion of norepinephrine or dopamine to maintain BP could open the blood–brain barrier and result in abnormal neurotransmissions in the brain of someone with schizophrenia.

Limitations. Several confounding factors, including delirium, septicemia, and schizophrenia itself, could present causal inference in this case, limiting our conclusions.

Conclusion. We observed a strong association between norepinephrine administration and psychosis in our patient with schizophrenia, who had been successfully treated with quetiapine for eight years prior to presentation. Quetiapine binds to a broad range of receptors, including adrenergic receptors. We believe that norepinephrine could be implicated in the pathophysiology of some patients with schizophrenia. Additional research investigating the potential role that norepinephrine antagonism could play in ameliorating the symptoms of schizophrenia is warranted.

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